REMARKS

Formal Matters

In the specification, the paragraphs reciting the priority information has been amended to drop the priority claim to the Jardieu *et al.* (PCT/US92/06860) lineage of applications.

Claims 1-19, 40, 44-65 remain in this application. Claims 20-39 and 41-43 were previously canceled. Claims 6, 8, 40, 44-48 and 50 have been withdrawn as the result of an earlier election of species, and there being at present no allowable generic claims. Claims 1, 11, 12, 19, 40, 44-50 are amended and new claims 51-65 are added. No new matter is added by the amendments.

Support for the amendments is found throughout the specification, and specifically at least as follows:

Claims 1 and 19: page 18, line 21 to page 19, line 2.

Claims 11 and 12: page 21, lines 20-34 and page 17, lines 15-24.

Claims 40-50: page 20, lines 30-31.

Claims 51-53: page 17, line 30 to page 18, line 5.

Claims 55-58: page 18, lines 1-5.

Claims 59-62: Page 18, lines 7-12.

Claims 63-65: Page 18, lines 14-19.

In view of restriction requirements in prior prosecution, Applicants retain the right to present withdrawn and/or cancelled subject matter in subsequent prosecution.

Priority

As noted previously, Applicants claim to priority from the Jardieu *et al.* has been dropped.

Judicially Created Double Patenting Rejection

Applicants respectfully request that the various double patenting rejections over various issued patents, pending applications and literature references (*i.e.*, USP 6,699,472; USP 6,685,939; 6,699,472; U.S.S.N. 11/013,966; U.S.S.N. 09/705,457; Larsen *et al., Asthma: Physiology, Immunopharmacology and Treatment* (3rd Int'l Symposium) (Ch. 15), Kay *et al.*, New York: Academic Press, pp. 245-262 (1984); Cockcroft *et al., J. Allergy Clin. Immunol.* (1987) 79: 734-740) be held an abeyance until the remaining rejections and objections are obviated.

Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 40-43 and 49 are rejected under 35 U.S.C. § 112, second paragraph, allegedly as being indefinite for failing to point out and distinctly claim the subject matter of the invention. Specifically, the Examiner asserts that the common understanding of the term "adjuvant" is a substance that enhances an immune response, whereas the agents disclosed in applicants claims are substances known to decrease it. The Examiner also objects to the notation of "beclomethasone, diproprionate" as separate elements of the Markush group in that "beclomethasone diproprionate" is a single compound.

In response, Applicants amendments have rendered the Examiner's comments moot.

Applicants respectfully request reconsideration and withdrawal of the rejection of Claims 40-43 and 49 under 35 U.S.C. § 112, second paragraph.

Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 40-43 and 49 are rejected under 35 U.S.C. § 112, first paragraph, allegedly as not being sufficiently described in a manner so as to convey possession of the claimed invention to one of ordinary skill. Specifically, the Examiner asserts that the various members of the Markush group do not appear to be disclosed as "adjuvants" in the specification, nor it is disclosed that they can be administered at any time other than concurrently with the anti-IgE antibody.

In response, Applicants respectfully disagree that the specification does not describe the administration "adjuvants" (now amended to read "therapeutic agent") at times before and after the administration of the anti-IgE therapeutic. For example, in the description of the "Experimental Results" section on page 21, lines 20-34, the protocol describes the administration of allergen one day prior to administration of anti-IgE therapy, with follow-up dosages weekly thereafter.

With respect to administration of therapeutic after allergen exposure, the specification contemplates biphasic dosing using a loading and a maintenance dose. On page 17, lines 15-24, the frequency of maintenance dosing can be from about every day to every 90 days, including weekly and biweekly. Read in context with the Experimental Results section which discusses allegen exposure prior to administration of therapeutic, the clear implication is that the administration of a maintenance dose would occur subsequent to allergen exposure, and one of ordinary skill would immediately recognize this to be so.

Applicants respectfully request reconsideration and withdrawal of the rejection of Claims 40-43 and 49.

Rejection Under 35 U.S.C. § 102(b) over Jardieu *et al.* (WO 93/04173)

Claims 40 and 43 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Jardieu *et al.* (WO 93/04173). Specifically, the Examiner asserts that Jardieu *et al.* discloses the administration of the combination of anti-IgE antibodies with antihistamines.

In response, Applicants' amendments render the Examiner's rejection moot.

The First Rejection Under 35 U.S.C. § 103(a) over Jardieu *et al.* (WO 93/04173) in light of Larsen *et al.*

Claims 1, 5, 7, 9-12, 16 and 18 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Jardieu *et al.* (WO 93/04173) in view of Larsen *et al., Asthma: Physiology, Immunopharmacology and Treatment* (3rd Int'l Symposium) (Ch. 15), Kay *et al.*, New York:

Academic Press, pp. 245-262 (1984). Specifically, the Examiner alleges that Jardieu *et al.* teaches a method of administering humanized anti-IgE antibodies for the therapy of IgE-mediated disorders, specifically with the antibody E25, which is also recited in the working examples. The Examiner further alleges that Larsen *et al.* teaches that LAR is an IgE mediated disorder because LAR is dependent upon the presence of antigen-specific IgE. As a result, the Examiner asserts, it would have been obvious to administer anti-IgE antibodies to teat LAR. The Examiner also asserts that while the combined teaching do not teach the reduction of IgE levels to the specific value of 40 ng/ml, a reduction to this level would be inherent in light of the identical antibody being described in both Jardieu *et al.*, and the working examples of the present application.

In response, Applicants agree that Jardieu *et al.* discloses the use of humanized anti-IgE antibodies to treat IgE-mediated disorders. However, Applicants do not agree that Jardieu *et al.* inherently describes the reduction of free IgE levels to a specific value of below 40 ng/ml. With respect to the claims as presently amended, Jardieu et al. dose not disclose the determine of baseline IgE levels prior to administration of IgE antagonists. Moreover, Applicants do not agree that Larsen *et al.* teaches to one of ordinary skill that LAR is necessarily an IgE mediated disorder. In responding, Applicants will first address the inherency question and then turn to the discussion of Larsen et al. and the connection between LAR and IgE.

The law of inherency

In relying upon the theory of inherency, the Examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art. *Ex parte Levy*, 17 U.S.P.Q. 2d 1461, 1464 (Bd. Pat. App. & Inter. 1990); M.P.E.P. § 2112. In order that a rejection based upon inherency may be sustained such inherency must be certain. *Ex part CYBA*, 155 U.S.P.Q. 756, 757 (P.O. Bd. App. 1967). An inherent limitation is one that is necessarily present; invalidation based on inherency is not established by "probabilities or possibilities. *Elan*

Pharmaceuticals Inc. v. Mayo Foundation, 64 U.S.P.Q.2d 1292, 1296 (Fed. Cir. 2002) (citing *Scaltech v. Retec/Tetra, LLC*, 51 U.S.P.Q.2d 1055, 1059 (Fed. Cir. 1999).

> Inherency, however, may not be established by probabilities or possibilities. The mere fact that a cetain thing *may* result from a given set of circumstances is not sufficient. [I]f, however, the disclosure is sufficient to show that *the natural result* flowing from the operation as taught would result in the performance of the questioned function, it seems to be well settled that the disclosure should be regarded as sufficient.
>
> *In re Oelrich and Divigard*, 212 U.S.P.Q. 323, 326 (C.C.P.A. 1981) (emphasis added).

While the above case law establishes and confirms that inherent anticipation requires an inevitability or certainty of the patented claim in light of the prior art disclosure - the more recent case of *Schering Corp. v. Geneva Pharmaceuticals, Inc.*, 67 U.S.P.Q.2d 1664 (Fed.Cir. 2003) applies these principles in a pharmaceutical context as well as clarifies what the law of anticipation by inherency does not require.

In *Schering*, Applicants Schering obtained a patent to a metabolite of the antihistamine loratadine (the '716 patent), also known as "DCL." This patent was filed more than one year after the issuance of the previous patent to loratadine (*i.e.*, the '233 patent). The claims to DCL were found to be inherently anticipated under 35 U.S.C. §102(b) by the disclosure of the '233 patent. Structurally, the only difference between loratadine and the metabolite was the presence of a hydrogen atom instead of a carboethoxy group on a ring nitrogen. In disposing of Schering's primary argument, the Federal Circuit repudiated and vacated the notion that inherent anticipation requires a recognition in the prior art. Eventhough the prior '233 patent did not recognize or expressly describe any compound identifiable as DCL, the court found anticipation by inherency because the ingestion of loratadine necessarily was metabolized into DCL in patients to whom it was administered. Interestingly, the court also discussed the requirements of a reference for a finding of anticipation - and confirmed the holding of *In re Donahue*, 67

U.S.P.Q.2d 1664 (Fed. Cir. 1985) that anticipation requires an enabling disclosure. *Schering* at 1670. Thus, because the '716 contained broad compound claims, they were anticipated by the '233 disclosure of the mere administration of loratadine to patients - the inherent result of which is the formation of DCL.

The present analysis

In light of the law discussed above, for inherent anticipation of the rejected claims to occur, the natural or inevitable result of the disclosure of Jardieu *et al.* is the initial determination of baseline serum IgE levels as well as the dosing thereagainst in order to achieve a therapeutic effect (*e.g.*, reduction of such serum IgE levels to 40 ng/ml or less). Moreover, it is only necessary that Jardieu *et al.* enable one of ordinary skill to practice this event, not that it be specifically described by Jardieu *et al.*

Applicants respectfully submit that the disclosure of Jardieu *et al.* does not inherently anticipate the invention. As a general initial comment, Jardieu *et al.* is a generic description of anti-IgE based therapeutics, whereas the present invention is a species description of a specific method of using anti-IgE therapeutics involving an initial determination of baseline IgE levels, and dosing on the basis of such baseline levels, in order to achieve a particularly-defined event (*e.g.*, reduction of free IgE to below 40 ng/ml) as well as to treat a specific form of asthma (late phase asthma). Jardieu *et al.* does not appreciate a methodology of first determining serum IgE levels and then dosing on the basis of such levels to achieve a therapeutic effect.

With respect to Claim 16, the reduction of free IgE to a specific level requires knowledge of the level of patient IgE prior to administration of the therapeutic, or "baseline IgE." Jardieu *et al.* does not describe or enable the measurement of baseline IgE. Because patient IgE can fluctuate from patient to patient, simple dosing on the basis of weight alone will not "necessarily" result in reduction of serum IgE to the specified level. Moreover, in order for any therapeutic effect to result from the administration of any anti-IgE therapeutic, one must have some knowledge of the relationship between IgE levels and asthma symptoms. Jardieu *et al.*

provides for anti-IgE therapeutics, but it does not establish how much of them should be administered to achieve clinical efficacy.

Thus, without knowledge of baseline IgE levels, and without the knowledge of how much anti-IgE therapeutic should be administered in order to achieve a reduction to a given fixed level (*i.e.*, 40 ng/ml), it simply cannot be said that administration of a given amount of IgE therapeutic will necessarily or inevitably result.

Next, Applicants turn to the issue of Larsen *et al.* teaching that LAR is an IgE-mediated disorder. The Examiner points specifically to the following passage to support his conclusion that Larsen et al. teaches that LAR is an IgE-mediated reaction:

> Thus, the date to date reviewed in this section demonstrate that the late asthmatic response can be passively transferred, the response is dependent on the presence of antigen-specific IgE, and the response is blocked in a dose-dependent manner by the presence of antigen-specific IgG.

Larsen at 253

Rebutting the Examiner's conclusion that Larsen *et al.* teaches that LAR is an IgE-mediated disorder, Applicants submit the declaration of Yamo Deniz, PhD. Based on his review and analysis of Larsen *et al.*, Dr. Deniz concludes that Larsen *et al.* does not reasonably teach that LAR in humans is an IgE mediated reaction. Dr. Deniz bases this conclusion on (1) that passive immunity is generally not an accurate model of the reactions associated with active immunity; (2) the particular passive immune model proposed by Larsen *et al.* lacks significant scientific controls; and (3) interspecies immunological differences, such as between rabbits and humans, is sufficiently divergent that an understanding of the immune mechanisms in one species would not necessarily transfer to another. Thus, on the basis of this declaration, Applicants have cast serious doubt, if not rebutted altogether, the finding that Larsen *et al.* teaches that LAR is an IgE-mediated reaction.

Applicants respectfully request reconsideration and withdrawal of the rejection of Claims 1, 5, 7, 9-12, 16 and 18 under 35 U.S.C. § 103(a).

The Second Rejection Under 35 U.S.C. § 103(a) over Jardieu *et al.* (WO 93/04173) in view of Larsen *et al.*, and further in view of Rup *et al.*, USP 4,940,782.

Claims 2, 14 and 15 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Jardieu *et al.* in view of Larsen *et al.* and further in view of Rup *et al.* (USP 4,940,782). Specifically the Examiner adds to the record in this rejection that Rup *et al.* teaches methods of administering anti-IgE antibodies (Col. 5, lines 50-65), including the administration of such antibodies in formulations comprising buffers and preservatives.

In response, Applicants respectfully submit the deficiencies of Jardieu *et al.*, and Larsen *et al.* have been discussed previously. Moreover, these deficiencies are not remedied by the teachings of Rup *et al.*

With respect to the Examiner's particular comments relating to Rup *et al.*, this reference does not disclose that anti-IgE therapeutics can be administered as a reconstituted lyophilized formulation. While the Examiner's comments indicating that the freeze-drying procedure would not materially alter the structure or therapeutic properties of the antibody, this comment does not address the fact that these references do not teach this manner of administration. Neither Jardieu *et al.* nor Rup *et al.* discloses or contemplated the measuring of baseline IgE level, and dosing relative to it in order to achieve a reduction resulting in therapeutic benefit.

Applicants respectfully request reconsideration and withdrawal of the rejection of Claims 2, 14 and 15 under 35 U.S.C. § 103(a) over Jardieu *et al.* in view of Larsen *et al.* and further in view of Rup *et al.* (USP 4,940,782).

The Third Rejection Under 35 U.S.C. § 103(a) over Jardieu *et al.*, (WO 93/04173) in view of Larsen *et al.*, in view of Rup *et al.*, and further in view of Jardieu 2 (USP 5,622,700).

Claims 3, 4 and 13 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Jardieu *et al.* in view of Larsen *et al.* and further in view of Rup *et al.* (USP 4,940,782). Specifically, the Examiner adds to the record in this rejection that the administration of antibodies to treat chronic disorders, such as asthma, may be accomplished through the administration of an initial loading dose followed by a subsequent maintenance dose, wherein the maintenance dose is lower than the loading dose.

In response, Applicants respectfully submit the deficiencies of Jardieu *et al.*, Larsen *et al.* and Rup *et al.* have been discussed previously. Moreover, these deficiencies are not remedied by the teachings of Jardieu2 *et al.* While Jardieu2 does describe the initial administration followed by a subsequent intermittent administration of anti-LFA-1 or anti-ICAM-1 antibody to treat psoriasis as well as prolonging graft survival in a host, this reference does not teach the application of this dosing methodology to IgE-mediated disorders. Specifically, neither reference discloses or contemplates the measuring of baseline IgE level, and dosing relative to it in order to achieve a reduction resulting in therapeutic benefit. Moreover, neither reference discloses or contemplates the reduction of such baseline IgE level to 40 ng/ml or less to achieve a therapeutic effect.

Applicants respectfully request reconsideration and withdrawal of the rejection of Claims 3, 4 and 13 are rejected under 35 U.S.C. § 103(a) over Jardieu *et al.*, (WO 93/04173) in view of Larsen *et al.*, in view of Rup *et al.*, and further in view of Jardieu2 (USP 5,622,700).

The Fourth Rejection Under 35 U.S.C. § 103(a) over Jardieu *et al.*, (WO 93/04173) in view of Cockcroft *et al., J. Allergy Clin. Immunol.* (1987) 79: 734-740

Claims 40 and 49 are rejected under 35 U.S.C. § 103(a) as being obvious over Jardieu *et al.*, (WO 93/04173) in view of Cockcroft *et al., J. Allergy Clin. Immunol.* (1987) 79: 734-740. Specifically, the Examiner adds to the record that Cockcroft *et al.* teaches the advantage of

administering multiple anti-asthmatic agents because often the administration of a single agent is inadequate to clinically treat symptoms. The Examiner further asserts that Cockcroft *et al.* discloses that steroids are desirable for combination therapy with anti-asthmatic agents because they can be administered prophylactically.

In response, Applicants respectfully submit that none of the cited references, either alone or in combination, suggest the administration of a combination of an anti-IgE antibody and steroid to treat asthma. To support a prima facie case of obviousness under 35 U.S.C. § 103, a combination of references must (1) first have some suggestion or motivation to combine the teachings of the references, existing either in the references themselves or in the knowledge available to one of ordinary skill, and (2) second there must be a reasonable expectation of success. M.P.E.P. § 2143. Moreover, the suggestion or motivation for the combination must be found in the art, and not in applicants' disclosure. *In re Vaeck*, 20 U.S.P.Q.2d. 1438 (Fed. Cir. 1991).

Turning to the case at hand, Jardieu *et al.* describes combination of anti-IgE therapeutics with the administration of other immune modulators such as gamma interferon, allergen desensitization and anti-histamines. While the first is another protein therapeutic, the second is a homeopathic remedy, while the third, antihistamines - is consistent with the known connection between IgE and EAR. However, as discussed by Applicants, the connection between IgE and LAR in human, until the disclosure of the present application was uncertain. Moreover, anti-IgE antibody is a protein-based biologic application, which is distinct from the small molecule bronchodilators and steroids described in Cockcroft *et al.* The distinct nature of these two classes of molecules is determinative that one of ordinary skill would not have combined the teachings suggested in Cockcroft *et al.* with the anti-IgE therapeutic in Jardieu *et al.* There was no suggestion or motivation in the art to combine the teachings of Jardieu *et al.* (*i.e.*, anti-IgE antibodies and antihistamines) with the small molecule bronchodialator and steroidal combinations described in Cockcroft *et al.* As Cockcroft *et al.* does not describe antihistamines, or especially combinations of antihistamines with bronchodialators and steroids, it does not

provide the motivation to combine antihistamines with any other asthma therapy. As a result, the Examiner has not made a successful prima facie case of obviousness. In any event, neither reference, alone or combined teaches the measuring of baseline IgE levels and then dosing relative to such levels to achieve therapeutic effect

Applicants respectfully request reconsideration and withdrawal of the rejection of Claims 40 and 49 under 35 U.S.C. § 103(a).

The Fifth Rejection Under 35 U.S.C. § 103(a) over Hardman *et al.* (EP 0 589 840) in view of Cockcroft *et al., J. Allergy Clin. Immunol.* (1987) 79: 734-740

Claims 40 and 49 are rejected under 35 U.S.C. § 103(a) as being obvious over Hardman *et al.*, (EP 0 589 840) in view of Cockcroft *et al., J. Allergy Clin. Immunol.* (1987) 79: 734-740. Specifically, the Examiner asserts that Hardman *et al.* teaches a method of administering anti-IgE antibodies to treat allergic asthma, while Cockcroft *et al.* discloses the administration of combinations of multiple asthmatic agents.

In response, Applicants respectfully submit that none of the cited references, either alone or in combination, suggest the administration of a combination of an anti-IgE antibody and steroid to treat asthma.

To support a prima facie case of obviousness under 35 U.S.C. § 103, a combination of references must (1) first have some suggestion or motivation to combine the teachings of the references, existing either in the references themselves or in the knowledge available to one of ordinary skill, and (2) second there must be a reasonable expectation of success. M.P.E.P. § 2143l. Moreover, the suggestion or motivation for the combination must be found in the art, and not in applicants' disclosure. *In re Vaeck*, 20 U.S.P.Q.2d. 1438 (Fed. Cir. 1991).

Turning the case at hand, an anti-IgE antibody of Hardman *et al.* is a protein-based biologic application, which is distinct from the small molecule bronchodilators described in Cockcroft. The distinct nature of these two classes of molecules is determinative that one of

ordinary skill would not have combined the teachings of using either component of the combination suggested in Cockcroft with the anti-IgE therapeutic in Hardman *et al.* There was no suggestion or motivation in the art to combine the teachings of Hardman *et al.* with those of Cockcroft *et al.* In any event, neither reference, alone or combined teaches the measuring of baseline IgE levels and then dosing relative to such levels to achieve therapeutic effect.

Applicants respectfully request reconsideration and withdrawal of the rejection of Claims 40 and 49 under 35 U.S.C. § 103(a) as being obvious over Hardman *et al.*, (EP 0 589 840) in view of Cockcroft *et al., J. Allergy Clin. Immunol.* (1987) 79: 734-740.

SUMMARY

Claims 1-19, 40, 44-50 and new claims 51-65 are pending in the application. Claims 20-39 and 41-43 were previously canceled without prejudice to later prosecution.

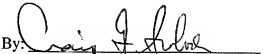
If in the opinion of the Examiner, a **telephone conference** would expedite the prosecution of the subject application, the Examiner is **strongly encouraged** to call the undersigned at the number indicated below.

This response/amendment is submitted with a transmittal letter and petition for a 3-month extension of time and fees. In the unlikely event that this document is separated from the transmittal letter or if fees are required, applicants petition the Commissioner to authorize charging our Deposit Account 07-0630 for any fees required or credits due and any extensions of time necessary to maintain the pendency of this application.

Applicants respectfully request that a timely Notice of Allowance be issued in this case.

Respectfully submitted,
GENENTECH, INC.

Date: **July 26, 2006**

By: 
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